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A CONSIDERATION OF THE PATHOGENESIS OF BACTERIAL MENINGITIS: REVIEW OF EXPERIMENTAL AND CLINICAL STUDIES

INTRODUCTION

Fifty years ago bacterial meningitis was studied intensively in both laboratory and clinic. Many illustrious investigators—Councilman, Flexner, Austrian, Wollstein, and Weed, to mention a few—lent themselves to the task of elucidating the pathogenesis, anatomical changes, and pathological physiology associated with these infections and devising effective forms of treatment for this almost invariably fatal disease. With the advent of antibiotics the outlook for patients with meningeal infections improved considerably, and concomitantly studies on experimental meningitis almost disappeared from the literature. It is significant that in a recent symposium on the cerebrospinal fluid a discussion of experimental meningitis was conspicuously absent.[104] In contrast to most other bacterial infections, however, nearly one quarter of patients with meningitis die despite optimal therapy with antibiotics.[80] The reason for this persistent mortality is not clear but stems in part, at least, from inadequate knowledge of the manner in which microbes produce infection within the subarachnoid space—their portal of entry, rate of growth, mode of dissemination within neural structures, action upon the normal exchange of metabolites between blood and cerebrospinal fluid, effect upon essential enzyme systems, and the mechanism by which they produce death. In our present state of knowledge, answers to most of these questions are not available.

It is the purpose of this brief review to assemble the pertinent information on the pathogenesis and physiology of meningitis, correlate it with certain phenomena observed clinically and raise questions which may lead to sound basic and clinical investigation of the mysteries beclouding the nervous system's response to infection. We have purposely limited the dis-

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cussion to acute bacterial meningitis and have restricted the references to pertinent experimental papers, omitting most clinical reports. This does not imply, of course, that bacterial meningitis serves as the prototype for infections of the pia-arachnoid by other agents. It is hoped, however, that an analysis of the factors mediating meningeal infections by bacteria may stimulate further thought and experimentation on the effect of other injurious stimuli, biological or physical, on the coverings of the nervous system.

EXPERIMENTAL MENINGITIS

A. *General considerations.* The earliest attempts to produce experimental meningitis in animals utilized infected cerebrospinal fluid from patients to establish an etiologic relationship and to fulfil Koch's postulates.[15, 31, 41, 52, 116, 153, 186] After it had been demonstrated conclusively that a number of common pathogenic bacteria such as the pneumococcus, meningococcus, and *Hemophilus influenzae* were capable of causing lethal inflammation of the meninges, meningitis in animals was employed experimentally to evaluate therapeutic regimens including serum,[60, 62, 196] subarachnoid lavage with antiseptic agents,[180] antibiotics,[145, 173] and proteolytic enzymes.[84]

One of the difficulties in interpreting the mass of experimental data in this field, has been the failure to achieve a standardized, reproducible experimental model such as acute pyelonephritis in rats,[22] pneumococcal peritonitis in rabbits,[18] or staphylococcal disease in mice.[130]

Before embarking upon a review of the literature, it seems worthwhile to propose certain definite criteria for the ideal infection to use as a standard of reference for comparison with previous studies:

1. The portal of entry and route of dissemination of the organism must be akin to those in man.
2. The parasite must be pathogenic for man as well as experimental animals.
3. The course of the disease must be relatively predictable and of sufficient duration to permit evaluation of therapy.
4. The disease must be reproducible within the limits of biological variation.
5. The lesions in the experimental infection must be morphologically similar to those in man.
6. The technique must be relatively simple.

Unfortunately, no single investigation has fulfilled these requirements, and, indeed, many questions need be answered before the criteria enumerated can be met. Our lack of understanding concerning the pathogenesis

of infections of the nervous system has led to many artificial studies in which the investigator has designed the experimental setting to conform to the expected results. Many of these investigations, however, furnish valuable clues which may not always supply direct answers but provide topics for further discussion and experimentation.

B. *Relationship between route of infection and development of meningitis.* The hypothesis that bacteremia per se may be attended by meningitis was examined with a variety of organisms. The early claims of Bull[25, 26] and Elser and Hutoon[52] that meningitis follows the intravenous inoculation of bacteria have not been substantiated.[4, 7, 85, 181, 192] As might be expected, the more remote intraperitoneal route has also failed to yield meningeal infection.[1, 31, 116] A single attempt to infect the central nervous system by direct injection of organisms into the carotid artery was unsuccessful.[76]

A more rational approach, predicated upon the clinical finding that meningococci were frequently harbored in the nasal passages of patients with meningococcal meningitis, consisted of the direct application of bacteria to the nasal mucosa of animals. However, meningitis did not occur.[7, 15, 116] It has long been evident that infections of the paranasal sinuses, middle ear, and mastoids can spread to the meninges. Attempts to duplicate this phenomenon in cats were only intermittently successful.[200] Furthermore, even in this study physical irritants such as iodine and mustard oil were used to facilitate passage from the frontal sinus to the meninges. Osteomyelitis was a frequent accompaniment of sinusitis in this experimental model, and it is conceivable that the bone rather than the sinus cavity served as the infecting focus. Southard and Keene were able to infect the meninges by intraorbital inoculation of bacteria,[162] but it is not clear from their report whether the injections were intraorbital or, in fact, intracerebral.

These studies indicate that the nervous system is admirably protected from infection by microorganisms in the blood stream and do little to establish the importance of "neighborhood infection" in the pathogenesis of meningitis. Furthermore, neither method has provided a suitable model for evaluating therapy.

More success has followed injection of bacteria directly into the lumbar subarachnoid space. Of historic interest are the studies of Councilman *et al.* who infected a goat by this route.[41] Subsequently, other investigators have utilized this method with a variety of organisms and species.[7, 61, 85, 192] Even man has served as an accidental subject in experiments of this type when clinical meningitis has followed lumbar puncture for spinal anesthesia and intrathecal therapy.[48] The offending organism is

usually one of the Gram-negative enteric bacilli, chiefly *Pseudomonas aeruginosa.* Stanley has reported 32 cases of iatrogenic Pseudomonas meningitis with a mortality of 40 per cent.[163]

In experimental animals a number of difficulties have been inherent in the installation of organisms directly into the lumbar sac. Firstly, the lack of predictability of the course of infection made response to therapy difficult to ascertain.[62, 198] For example, Flexner, employing meningococcus, was impressed with the acute course of the disease.[61] On the other hand, Lamar[109] and Idzumi[85] were able to produce a protracted illness with the pneumococcus. Death in the acute cases was probably due to bacteremia, but bacteriological confirmation of this was sparse. Secondly, spinal cord injury has been frequent and bacteria have often been injected into the cord.[7, 85] Lastly, the small size of the lumbar sac in most species has led to inaccurate placement of bacterial inocula as well as a paucity of spinal fluid for serial studies.

Some of these objections can be overcome by employing suboccipital puncture with introduction of bacteria into the cisterna magna. The technique of cisternal puncture was first employed in animals by Dixon and Halliburton in 1913[48] and in man by Wegeforth *et al.*[188] several years later. Subsequently, this method was used extensively because of the accessibility of the subarachnoid space in this area and the ease with which repeated samples of spinal fluid can be obtained.[18, 19, 20, 56, 77, 87, 93, 104, 145, 166, 167, 173, 202] The main disadvantage of this experimental model is the frequent occurrence of bacteremia and early death,[56, 104, 145, 166, 173] raising the question whether death in these animals was a consequence of the inflammatory changes in the neuraxis or overwhelming sepsis. A similar problem may, in fact, exist in man, and Daniels has postulated that death in meningococcal meningitis was related to the "toxic" effect of bacteremia as much as meningitis.[45] This conflicts with the findings of Alexander *et al.,* who state that mortality in pneumococcal meningitis could not be correlated with bacteremic spread.[3] The prognostic implication of bacteremia in clinical meningitis deserves further study.

In animals, in addition to the acute septicemic form, the intracisternal instillation of bacteria may be followed by a chronic indolent infection of the meninges.[56, 167] The persistence of the inflammatory process may be related to subarachnoid blockage by large quantities of exudate or to the development of abscesses within the parenchyma of the spinal cord.[166] Since many of these infections were created for the purpose of analyzing some specific therapeutic regimen, the chronic exudative type is to be preferred to the acute septic type. Unfortunately, there is no way to predict

in the individual animal which course the infection will follow. By injecting ground jellied agar in combination with *Pseudomonas aeruginosa,* Hamburger was able to achieve a chronic exudative infection regularly.[77] Another group of animals infected intracisternally have had a relatively prolonged illness terminating in recovery or death. However, exudation was not a feature of their disease and at autopsy only minimal morphological changes were present in the nervous system but, interestingly enough, heart blood cultures were positive. Although endocarditis was not described, one wonders whether it may have been present. The course of these animals is reminiscent of that of patients who recover from pneumococcal meningitis only to succumb to endocarditis.[8]

Minor difficulties which have been encountered with the intracisternal route are extravasation of the inoculum into the surrounding soft tissues and direct trauma to the medulla oblongata.[142]

Intradural administration of bacteria through a trephine is another technique for infecting the meninges.[15, 186] This method affords increased accuracy by permitting direct visualization of the meninges but is somewhat tedious. Manwaring attempted placement of virulent tubercle bacilli into the basilar cisterns by puncturing the frontal lobes with a long needle.[135] As pointed out by Austrian,[8] however, this maneuver was accompanied by extensive damage to cerebral parenchyma.

Compared to its extensive use in the investigation of neurotropic viruses, direct intracerebral inoculation of bacteria has been used rarely.[54, 70, 134, 136] In most animals, either transient neurological disturbances or a diffuse cerebritis with fulminating septicemia are observed. Localization of the infection with abscess formation was possible only when the cerebral parenchyma was injured by needle puncture several days before bacteria were reinjected into the site of previous trauma.[70, 134, 136]

Flexner and Amoss performed a series of classical experiments in monkeys in which the combination of sterile aseptic meningitis and viremia was used to induce clinical poliomyelitis.[63, 65] In a number of studies in which bacteria rather than viruses were given intravenously following aseptic meningitis, meningeal infection occurred only sporadically.[4, 7, 85, 151] Sterile inflammation of the meninges can regularly be observed following the intrathecal administration of saline, serum, and a variety of other substances and probably enhances the passage of pathogens from blood to nervous system. Clinically it appears to be of little significance since bacterial superinfection in patients with aseptic meningitis is rare.

The studies described thus far do not elucidate the train of events in the pathogenesis of meningeal infections in man and, except for meningitis

secondary to a neighboring focus and iatrogenic infection following lumbar puncture, have little applicability to human disease. While there is no direct evidence that microorganisms reach the meninges via the blood stream, the frequency with which meningeal infection is preceded by bacteremia suggests that the hematogenous route may be an important pathway by which bacteria reach the nervous system. This thesis gains support in the studies of Weed *et al.*, relating alterations in cerebrospinal fluid dynamics during experimental bacteremia to the development of meningitis.[179, 181] When cerebrospinal fluid was removed from cats immediately preceding or following the intravenous introduction of a virulent culture of *B. lactis aerogenes,* generalized leptomeningitis developed, usually within 24 hours. Control animals given twice the intravenous dose invariably remained well. *B. lactis aerogenes* was used in the majority of experiments, but infection could be produced by several other bacterial species. This phenomenon did not appear to be peculiar to the cat since other animals could also be infected.

The obvious explanation for these results is that trauma to small meningeal blood vessels at the time of lumbar or cisternal puncture provided access for bacteria but careful morphological studies failed to substantiate this.[9] Furthermore, infusion of hypertonic solutions, compression of the jugular veins, and transient cardiac standstill during bacteremia were also followed by meningitis, indicating that direct injury to nervous structures was not a sine qua non in the development of this infection.[181] Weed postulated that the occurrence of infection was facilitated by the transient lowering of cerebrospinal pressure associated with these procedures. Unfortunately, there are no data to support this hypothesis because no accurate measurements of spinal fluid pressure were made. Since jugular compression, which is usually attended by an abrupt rise in cerebrospinal fluid pressure, had the same effect as procedures which presumably resulted in cerebrospinal hypotension, one wonders whether the rate of change rather than the direction may not be of importance. A crucial experiment would be to determine whether the re-injection of cerebrospinal fluid following its removal during bacteremia would prevent meningeal infection. Unfortunately, data on this point are scanty.

The applicability of Weed's experiments to the pathogenesis of the disease in man is difficult if not impossible to determine. Even if it were postulated that bacteremia antedated meningitis under natural conditions, the magnitude of change in spinal fluid dynamics might be insufficient to facilitate infection. Of more clinical significance is the possible danger of diagnostic lumbar puncture during bacteremia. Wegeforth and Latham per-

formed lumbar punctures in 93 patients with suspected meningitis.[184] In 55 of these, the cerebrospinal fluid was normal. Six patients had meningococcemia or pneumococcal bacteremia at the time of lumbar puncture, and five of the six subsequently developed meningitis. On the basis of these findings, the authors condemn diagnostic lumbar puncture in the absence of strong clinical indications. Remsen shared this viewpoint and added a case of streptococcal meningitis occurring under similar circumstances.[158] It seems likely that these few cases are not representative of the over-all clinical experience, and that the occurrence of meningitis following lumbar puncture during bacteremia is relatively rare. Pray lends support to this by presenting evidence that the incidence of meningitis in children with pneumococcal bacteremia is not increased by lumbar puncture.[146] Compared to the risk of missing the diagnosis of meningitis by omission of lumbar puncture, the chance of developing meningitis following the procedure is small even in the presence of bacteremia, and there are not sufficient data to consider "suspected or documented sepsis" as a contraindication to lumbar puncture.

Although not strictly pertinent to the subject of acute bacterial meningitis, the studies of Rich and McCordock based upon some of these early negative experiments deserve mention.[151] These investigators noted a rather persistent discrepancy between the age of the visceral lesions in miliary tuberculosis and the tubercles in the meninges, the latter appearing more acute than the former. This finding suggested to them that the meninges were probably not seeded with tubercle bacilli by the hematogenous route. Furthermore, they were consistently unable to produce meningitis by the intravenous injection of virulent tubercle bacilli into hypersensitive animals despite the fact that massive visceral tuberculosis invariably developed. On the other hand, intrathecal administration of acid-fast organisms resulted in infection of the meninges. These experiments indicated that the pia-arachnoid was infected from contiguous foci in the underlying cerebral parenchyma, and this impression was confirmed by the finding of tuberculomata in the cerebral cortices of 77 of 82 patients with tuberculous meningitis. Unfortunately, no such clinicopathological relationships have been derived in acute bacterial meningitis, and it is not known whether infected CSF serves as a focus for infection of the brain and spinal cord or whether the reverse situation obtains.

C. *Causative pathogen.* Meningitis in animals has been produced experimentally by most of the organisms which cause the disease in man. The common human pathogens *D. pneumoniae, N. intracellularis, H. influenzae,*

and *Staph. aureus* have been used most often. Gram-negative enteric bacilli have been the subject of a few studies.[56, 77, 151]

In man there is good correlation between the etiological pathogen and the clinical setting. Thus, pneumococcal meningitis is frequently a sequel to infection of the paranasal sinuses, mastoids, and pleural space; the meningococcus tends to produce a fulminating illness in an epidemic setting; hemophilus shows predilection for children, staphylococcal meningitis is prone to occur with cavernous sinus thrombosis or epidural abscess, and Klebsiella meningitis is most often seen in diabetics or after head trauma.[162a, 173a] Similar differences have been noted in some animal experiments. Although different animals were employed, pneumococcal meningitis[85, 109] appears to run a more protracted course than the disease produced by the meningococcus.[61] Stewart found that type II pneumococcal meningitis was characterized by formation of a heavy fibrin exudate and rapid development of subarachnoid block, while type I caused a septicemic illness associated with minimal exudation.[167, 169]

Most cases of iatrogenic meningitis are caused by Gram-negative organisms rather than other human commensals.[48] This observation in conjunction with experimental evidence suggests that Gram-negative bacteria may possess a high degree of virulence for the meninges.[56] The capacity of these organisms to elaborate an endotoxin may account for the increase in virulence. Pertinent to this point are the studies of Branham and co-workers in rabbits which suggest that the damage to the meninges following injection by the intracisternal route may be due to a toxic product of the pathogenic bacterium rather than the intact organism.[18–21] They found that purulent or fibrinopurulent meningitis occurred with living meningococci as well as organisms which had been boiled or passed through a Berkefeld N filter and they were unable to distinguish clinically or pathologically between the infections produced by the different preparations. Direct instillation of highly purified endotoxin from *Salmonella abortus equi* and *Shigella flexneri (type Z)* into the cisterna magna of dogs also resulted in marked cerebrospinal fluid pleocytosis.[142]

The virulence of the infecting organism is enhanced by serial intrameningeal passage.[4, 57, 145, 173] In this respect the meninges resemble other tissues. This phenomenon is independent of the species and organism employed. Its clinical significance in man is unknown.

D. *Susceptible host.* Meningitis occurs naturally in a wide variety of animals. For example, spontaneous meningococcal and pneumococcal meningitis has been described in horses, calves, and goats; young animals appear to be more vulnerable.[84] Pseudomonas has been incriminated as a cause

of meningitis in pigs with infectious rhinitis.[106] In view of the wide natural host range of meningeal infections, it is not surprising that the disease has been produced with ease in guinea pigs, rabbits, monkeys, dogs, and cats. The last two lend themselves well to experimentation. Their relatively large size minimizes the difficulty of lumbar puncture encountered in smaller species and also furnishes an adequate amount of spinal fluid for examination. Rabbits are poor experimental subjects since many have sustained cord damage at time of lumbar puncture and cerebrospinal fluid has been difficult to obtain in sufficient quantity. This species is also highly susceptible to the lethal effect of bacteremia with certain organisms.[7, 85, 166]

Different species may be particularly resistant to bacterial infection with certain organisms. For example, the dog tolerates pneumococcal meningitis better than the rabbit.[85] There is little other information concerning differences in the susceptibility of individual species to infection of the meninges.

THE EFFECT OF INFLAMMATION ON THE PERMEABILITY OF THE MENINGES

A. *General considerations.* The mechanisms controlling the passage of substances in and out of the nervous system are complex and poorly understood. Functionally, two sites of exchange have been postulated. One, which encompasses the entire neuraxis, is concerned with a transfer of organic and inorganic materials between the plasma and the cerebrospinal fluid—the blood-cerebrospinal fluid barrier. The other, termed the blood-brain barrier, is the locus of interchange between the blood stream and neural parenchyma. The anatomical location of these two barriers, their relationship to one another, and their basic physiological actions are controversial and not germane to the present discussion. Suffice it to say, both are profoundly altered by inflammation of the meninges. These changes in permeability may contribute to the aberrations of the spinal fluid in meningitis and may affect the course of the disease. Finally, the passage of drugs into the nervous system is controlled to a large extent by these barriers and any variation in the entry of chemotherapeutic agents is of obvious importance. In the following section, the effect of inflammation on the permeability of these barriers to a variety of exogenous and endogenous substances will be discussed.

B. *Exogenous substances.* 1. Inorganic ions. A number of inorganic substances normally not found in the spinal fluid have been given to patients and animals with meningitis to determine whether they could be recovered in the spinal fluid. Of the many anions tested,[97] studies with bromide[83, 177] and radioactive phosphorus[58] have been most valuable. The bromide test

involves the oral or intravenous administration of sodium bromide followed by simultaneous measurements of this ion in the serum and spinal fluid after equilibrium is established. Normally the ratio between blood and cerebrospinal fluid bromide is 2.6 and remains remarkably constant. With the development of meningitis, the ratio approaches unity and rises again as healing takes place.[160, 172]

The distribution of radioactive phosphorus (P^{32}) has been measured in experimental staphylococcal and streptococcal meningitis in rabbits.[58] Within 24 to 36 hours after the induction of infection, the P^{32} concentration in the cerebrospinal fluid of animals with meningitis was three times that of the controls. The P^{32} concentration in the cerebral parenchyma had risen two-fold.

2. Dyes. The historic observation of Goldmann that trypan blue given parenterally was unable to penetrate into the nervous system initiated the concept of the blood-brain barrier and prompted investigation of a number of organic dyes as indicators of meningeal permeability.[78] Koyama reviewed the passage of 52 dyes into the cerebrospinal fluid of rabbits and found that their concentration was increased in meningitis.[107]

Sodium fluorescein (Uranin) also lends itself to measurement of the integrity of the blood-cerebrospinal fluid barrier. Following oral or parenteral administration, little is found under normal conditions, but it is readily detected in patients with bacterial or tuberculous meningitis.[17, 58, 88, 111] Similar results have been reported in syphilis of the nervous system.[157]

Of interest are a few experiments in which organic dyes were utilized to determine passage from the spinal fluid to the blood, and it is noteworthy that some substances which gain access from blood to cerebrospinal fluid with difficulty pass in the reverse direction with ease. Thus, trypan blue given intrathecally is detectable in the blood stream shortly after instillation.[78] Similarly, normal infants given phenolsulfonphthalein (PSP) intrathecally excrete the dye in the urine shortly thereafter.[44] Limited studies suggested that intrathecal PSP may be retained in the subarachnoid space when the meninges become involved by disease.[128] This might be of clinical significance since therapeutic agents might be handled in similar fashion.

3. Toxic products of bacteria. It is conceivable that the ability of bacteria to cause infections in the nervous system is related not to their invasiveness but rather to the ability to elaborate endotoxins which might facilitate their passage from blood to brain. This may account for the meningeal virulence of *B. lactis aerogenes* described by Weed, and, more importantly, for the propensity of *Neisseria intracellularis* to cause meningitis.

The intracarotid administration of endotoxin has been shown to enhance the passage of fluorescein into the brain of the rabbit.[51] When the toxin was given intravenously, there was also some increase in passage of the dye from blood to CSF although this occurred only after a lag period of two hours.[144] On the other hand, administration of typhoid vaccine to dogs four hours preceding the intravenous injection of pneumococci, followed by lumbar puncture, did not increase the incidence of pneumococcal meningitis in these animals.[142] These experiments are far from conclusive, and the role of endotoxins in the pathogenesis of bacterial meningitis deserves further study. In contrast to endotoxins of Gram-negative bacteria, the exotoxins of diphtheria, tetanus, and staphylococcus were not injurious to the blood-brain barrier.[23]

4. Drugs. The passage of drugs into the spinal fluid under normal and abnormal conditions has received intensive study. The present discussion will limit itself to the passage of antimicrobial agents in meningitis. Aseptic meningitis facilitated the passage of arsphenamine into the cerebrospinal fluid[129] but did not enhance its deposition in the brain or spinal cord.[165] Binding by plasma proteins limits the ingress of sulfonamides into the spinal fluid, but usually sufficient quantities enter to achieve theoretically adequate therapeutic levels.[78] Sulfanilamide penetrates into the cerebrospinal fluid most effectively, and, after equilibrium has taken place, the cerebrospinal fluid concentration is equal to that of the blood.[78]

Since penicillin is the drug of choice in the treatment of Gram-positive coccal meningitis, its passage into the cerebrospinal fluid has received wide attention. Many studies employing small dosages of the drug attest to the relative impermeability of the blood-cerebrospinal fluid barrier to penicillin.[89, 90, 121, 148] When large amounts of penicillin are given parenterally, there seems to be a slight increment in the amount of drug found in the cerebrospinal fluid, but this is not a linear relationship.[16, 149, 154] The data provided by these studies are limited and require confirmation. Fortunately, there is general agreement that transfer of penicillin from blood to spinal fluid is increased in meningitis.[89, 90, 154] Little is known about cerebrospinal fluid level of the drug during acute infections, but the striking decrease in mortality observed with the use of this drug provides prima facie evidence that in the majority of cases therapeutically effective concentrations are reached. Based on a comparison with several series of patients with pneumococcal meningitis treated with parenteral penicillin it can be concluded that the addition of the drug intrathecally does not exert a major effect.[27, 118, 150] However, in occasional patients with peripheral circulatory collapse, intrathecal administration may offer a distinct advantage.

Under normal conditions streptomycin does not diffuse readily into the cerebrospinal fluid, but its passage is enhanced by meningeal inflammation.[24, 79, 201] Although it was once considered necessary to administer streptomycin intrathecally, this practice is distinctly hazardous and should be avoided.[29, 191] Fortunately, the advent of isoniazid in the treatment of tuberculous meningitis and chloramphenicol for infections caused by *H. influenzae* has led most clinicians to abandon the use of intrathecal streptomycin. There is little doubt, however, that prior to utilization of massive parenteral chemotherapy, and the advent of more effective drugs, the direct instillation of antimicrobials into the subarachnoid space was often lifesaving.[188a]

The tetracyclines are capable of traversing the blood-cerebrospinal fluid barrier, tetracycline being the most diffusable and oxytetracycline the least.[190] Normally, the tetracycline level in the cerebrospinal fluid is one-tenth of that in the blood.[190] Infection enhances the permeability of the meninges to oxytetracycline and, presumably, to the others in this group.[203]

Chloramphenicol is regularly detected in the cerebrospinal fluid when blood levels greater than ten micrograms per ml. are reached, and the concentration in the spinal fluid is approximately 25 per cent of that in the blood.[155] The availability of chloramphenicol as the highly soluble succinate salt makes blood levels of this magnitude easily attainable.

Bacitracin diffuses readily when the meninges are inflamed but poorly when they are normal.[173] In contrast, isoniazid is widely distributed throughout the body including the spinal fluid.[183] Measurement in a single patient with tuberculous meningitis suggested that hydrocortisone may enter the cerebrospinal fluid more readily than normal in this infection.[43]

The levels of various drugs in the CSF should not be equated with those of nervous tissue. A few studies which measure the passage of drugs into the cerebral parenchyma have been done[108, 189] but simultaneous measurements of drug levels in brain and cerebrospinal fluid have been limited and more are needed.

C. *Endogenous substances.* As has been pointed out, inflammation not only promotes the transport of foreign materials into the nervous system, but also disturbs the equilibrium between substances normally present in blood and spinal fluid. Among these are protein, sugars, organic acids, and various inorganic ions.

1. Protein. Elevation of the cerebrospinal fluid protein is typical of bacterial meningitis. The nature and origin of this protein have not been clearly defined. In the normal dog, there is active exchange of radioactive iodinated serum albumin between the plasma protein pool and the spinal

fluid.[59] These studies have not been performed in patients or animals with bacterial meningitis. However, electrophoretic studies demonstrating an increase in the cerebrospinal fluid albumin fraction in the early stages of human meningitis suggest that infection increases meningeal permeability to serum protein.[101, 112, 127] As the infection progressed, increases were noted in all fractions of the cerebrospinal fluid globulin; with subsidence of meningitis, the elevation became localized to the gamma globulin fraction.[127]

Increased vascular permeability and cellular breakdown have been held to be the cause of the protein elevation in meningitis.[68] On the other hand, a portion of this protein may emanate from nervous tissue per se. In support of this idea are the experiments of Mutermilch demonstrating the capacity of the nervous system to form antibodies to sheep red cells given intrathecally.[135, 136] Furthermore, elevation of the CSF gamma globulin without concommitant increase of serum gamma globulin has been reported in multiple sclerosis and central nervous system lues.[92, 199] The increased cerebrospinal fluid gamma globulin found late in meningitis may represent an immune response of the nervous system.

Pertinent to this point is the observation that seronegative patients with tuberculous, meningococcal, and lymphocytic nonbacterial meningitis occasionally have a transiently positive Wasserman test in the CSF.[158a] This suggests that under certain conditions neural tissues may elaborate a reagin which combines with alcoholic beef heart extract. This hypothesis would be more convincing were it not for the fact that some patients with seropositive latent lues also develop positive CSF complement fixation tests for syphilis during the course of bacterial or viral meningitis. In these circumstances, passage of the reagin from blood to CSF must surely be a consequence of a break in the blood-CSF barrier.

2. Sugar. A depressed spinal fluid sugar is the hall-mark of bacterial meningitis. Hypoglycorrhachia of lesser degree has been described in tuberculosis, syphilitic[132] and yeast meningitis, sarcoidosis of the nervous system,[140] diffuse leptomeningeal carcinomatosis,[14, 49, 170] and subarachnoid hemorrhage.[123] The low cerebrospinal fluid sugar is the single most important difference between tuberculous and viral meningitis.

Normally the level of glucose in the spinal fluid closely parallels that in the blood.[46, 67] For example, artificially induced hyperglycemia in man and animals is accompanied by a rise in the cerebrospinal fluid sugar. It is noteworthy, however, that the maximum increase in the cerebrospinal fluid glucose is not observed for several hours following hyperglycemia.[30, 75, 156] Conversely, hypoglycemia is associated with a fall in cerebrospinal fluid glucose.[46, 94]

The mechanism governing the disappearance of cerebrospinal fluid sugar in bacterial meningitis has not been clearly elucidated, and the relative importance of cells, bacteria, changes in meningeal permeability, and accelerated utilization by neural tissue in the genesis of hypoglycorrhachia remains poorly defined. On the basis of existing evidence, however, certain categorical statements can be made.

1. Clinical and experimental bacterial meningitis is characterized by a pleocytosis, presence of bacteria, and a depression of spinal fluid sugar.
2. This fall in cerebrospinal fluid sugar is not observed in aseptic or viral meningitis despite the presence of leukocytes. This has been established both in animals,[10, 74, 82] and in man.[175]
3. Incubation of sterile, cell-free spinal fluid at room and body temperatures for prolonged periods has not been attended by a decrease in sugar content.[10, 37, 55, 81, 82, 98, 122, 134, 138]
4. The addition of cells to sterile cerebrospinal fluid *in vitro* reduces the amount of available sugar,[10, 74, 81, 82, 98, 122, 161] and the degree of glycolysis is directly proportional to the number of cells. Polymorphonuclear leukocytes appear to utilize glucose more avidly than lympocytes.[81, 122, 161]
5. When pneumococci were incubated in cell-free, sterile spinal fluid, no glycolysis occurred unless the number of organisms far exceeded that present in experimental infection in dogs.[74] The *in vitro* utilization of glucose in cerebrospinal fluid by several other bacterial species has yielded inconsistent results.[10, 81, 98, 122]

The discrepancy between the normal sugar levels in aseptic meningitis and the capacity of leukocytes to utilize sugar *in vitro* has led to the suggestion that the inflammatory process makes the meninges more permeable to glucose. This in turn permits replenishment of cerebrospinal fluid glucose from the blood. Another explanation which comes to mind is that the exudate in most instances of aseptic meningitis consists predominantly of lymphocytes which use but little glucose.

In view of the fact that bacteria are essential for hypoglycorrhachia *in vivo,* it seems anomalous that the number of organisms necessary to produce a comparable fall *in vitro* does not manifest itself *in vivo.* On the basis of these experiments, one cannot attribute the decreased sugar in meningitis to either cells or bacteria alone. It is conceivable that the glycolytic power of bacteria may be enhanced by the presence of cells. This has not been tested under experimental conditions *in vitro.* That it may occur, however, can be discerned from recent studies of Petersdorf *et al.*

who produced pneumococcal meningitis in dogs made leukopenic by total body irradiation.[148] These animals were unable to respond to the meningeal infection with a pleocytosis and experienced no fall in cerebrospinal fluid sugar despite the presence of a large number of organisms. Changes in the permeability of the blood-cerebrospinal fluid barrier in this situation are probably of minor consequence.

Some evidence exists that the blood-cerebrospinal fluid barrier may be altered in the course of tuberculous meningitis. This is not unexpected in the face of the slow utilization of glucose by the tubercle bacillus[117] and the predominantly lymphocytic response. Furthermore, sugar introduced intrathecally into patients with tuberculous meningitis disappears more rapidly from the spinal fluid than could be explained by utilization by cells or acid-fast bacilli.[110, 178, 185] These investigations imply more rapid transfer of sugar from the spinal fluid to the blood stream. It has also been noted that hyperglycemia in tuberculous meningitis is paralleled by a rapid rise in cerebrospinal fluid glucose, connoting a disruption of the blood-cerebrospinal fluid barrier.[110]

3. Organic metabolites. Lactic acid in the spinal fluid rises in purulent meningitis and a variety of other conditions.[72, 139, 197, 198] The elevation appears to vary directly with the cell count and correlates poorly with reduction in the cerebrospinal fluid glucose. It seems likely that the organic acid is a by-product of cellular breakdown.[47, 105]

Ethyl alcohol is increased in the spinal fluid of some patients with cryptococcal meningitis who also have a low cerebrospinal fluid sugar.[174] This ingenious observation, which facilitates the differentiation between tuberculous and cryptococcal meningitis, is based on the fact that ethanol is the end product of glycolysis by yeast forms.

4. Inorganic ions. The decrease in the cerebrospinal fluid chloride in meningitis is probably a reflection of the loss of this anion from the extracellular fluid since the ratio of cerebrospinal fluid to blood chloride remains fixed.[115, 198] Cheek has suggested that the hypochloremia in tuberculous meningitis is a consequence of metabolic alkalosis and hypotonic expansion of the extracellular compartment.[82, 83]

The concentration of sodium in the spinal fluid is also dependent upon the serum concentration. Experimental hypernatremia results in a rise in cerebrospinal fluid sodium.[40] This may be a reflection of increased permeability since it has been demonstrated that hypernatremia in cats has been associated with profound damage to neuronal tissue.[118] Further support for enhanced passage of sodium into the spinal fluid following meningeal injury may be adduced from the finding that cerebrospinal fluid levels

of radioactive sodium in tuberculous meningitis are higher than in controls.[18] In contrast to sodium, potassium in the spinal fluid does not vary with alterations of the serum potassium.[40] This cation has not been studied in meningitis.

Elevations in the cerebrospinal fluid phosphorus have been reported in meningitis,[35, 38, 121] as well as in a variety of other neurological disorders.[70] Its significance is not known. There is a decrease in magnesium in the cerebrospinal fluid of patients with chronic meningitis,[119] but calcium is elevated.[38, 121] Both ionized and protein-bound calcium contribute to this rise.

THE ROLE OF HOST FACTORS IN MENINGITIS

A. *Anatomical and physiological defense mechanisms.* Compared to other bacterial infections, meningitis is a rare disease, and bacterial pathogens isolated in meningitic infections much more frequently parasitize other sites in the body. Of the bacteria most commonly found in meningitis only *Neisseria intracellularis* exhibits particular affinity for the nervous system. However, this organism is most often a benign commensal in the upper respiratory tract and only rarely is a cause of clinical infection. The implications of these clinical observations are that the central nervous system is extraordinarily well protected from infections, a most fortunate circumstance considering the high mortality and disastrous sequelae of meningitis. Not the least important of these protective mechanisms is the anatomical position of the nervous system. Encased by bone and connective tissue, it is well shielded from external stimuli, including bacteria. In many instances of meningitis, a specific disruption of this anatomical barrier such as fracture, osteomyelitis, or dural tear can be demonstrated.

Functionally, the nervous system is also protected from invasion of bacteria by unique filtering mechanisms—the blood-CSF and blood-brain barriers. As has been mentioned, these barriers are poorly defined anatomically and physiologically but there is little question about the remarkable control which they exert upon the passage of metabolites into and out of the nervous system. At the same time the entry of noxious substances appears to be prevented. The precise alterations in these barriers in response to infection remain ill defined but are probably most important.

B. *Susceptibility of neuronal tissue.* Little is known about the susceptibility of neuronal tissue to bacterial infection. It is not known, for example, whether there are factors indigenous to the cellular elements in the brain, spinal cord, and meninges which make them react in a particular manner to certain species of bacteria. *B. lactis aerogenes* has been said to be particu-

larly virulent for the meninges, but there is no evidence based upon *in vitro* studies that this tissue supports the growth of the pathogen better than others elsewhere in the body. Although poorly phagocytic normally, the arachnoid lining cells are capable of transformation into effective phagocytes under conditions of extreme irritation.[182] The nature of these irritating stimuli has not been elucidated and, in general, little is known about the role of phagocytosis in infections of the meninges. Lysozyme in the CSF is known to be increased in bacterial meningitis; this is probably merely a reflection of the presence of polymorphonuclear leukocytes, which are rich in this enzyme.[147] It is conceivable, however, that lysozyme is a product of injury to nerve cells per se.

C. *The inflammatory reaction in the meninges.* While it seems clear that there are potent defense mechanisms to prevent the entry of pathogenic bacteria into the CNS, once infection is established host defenses are quite inadequate. Proof of this statement lies in the high mortality prevalent prior to the use of antibiotics. Even with appropriate chemotherapy and sterilization of the CSF, the mortality rate remains close to 25 per cent. The mechanism of death in meningitis under these circumstances is not well understood. Endocarditis and pneumonia may account for some therapeutic failures; the majority, however, are probably related to the fact that the inflammatory reaction, normally an important cog in the defense to infection, may be distinctly deleterious in the cranial cavity. In most loci the inflammatory exudate or pus is easily removed by drainage, expectoration, or micturition depending upon the site of the infection. These avenues of escape are not available in acute leptomeningitis, and resolution and absorption of inflammatory cells are the only means for recovery. Failure to remove the exudate may result in an increase in intracranial pressure or development of subarachnoid block, either of which can be fatal. Inflammatory exudates may also adversely influence the action of antibiotics; Wood and Smith demonstrated in experimental pneumococcal pneumonia that antimicrobial activity was greater at the periphery of the lesion, where bacteria were actively multiplying and cellular exudation was sparse, than in the center loaded with masses of inflammatory cells and dead organisms.[195]

ACTH and cortisone have been employed in bacterial meningitis to mitigate the inflammatory response and to prevent some of these complications. Ribble and Braude reported recovery in 11 of 12 patients with pneumococcal meningitis treated with penicillin and adrenal cortical hormones, a therapeutic result superior to any group treated with penicillin alone.[150] However, this study contained no controls. More recently, Lepper and Spies treated alternate patients with pneumococcal meningitis with adrenal steroids and penicillin and were unable to demonstrate that the hormones exerted a

beneficial effect.[114] There seems to be little doubt that adrenal steroids have favorably affected the course of tuberculous meningitis and should be used in addition to chemotherapy.[90] In the face of these inconclusive data the effectiveness of adrenal hormones as therapeutic adjuncts must remain *sub judice*. There is good theoretical basis for their use not only to minimize the inflammatory response but also to modify the acute hypersensitivity reaction to bacterial products which may play a role in some types of bacterial meningitis (*vide infra*). Further therapeutic trials with adrenal hormones seem indicated particularly since it appears that they are not harmful in acute bacterial infections of man when proper antibiotics are administered.[176]

The instillation of the proteolytic enzymes, streptokinase-dornase, into the subarachnoid space to aid in resolution of the thick proteinaceous exudate has received wide attention. The results have not been impressive and sometimes the constitutional reaction to these drugs has been extraordinarily severe. In a recent enthusiastic report Tillet described the action of these enzymes in pneumococcal meningitis.[80]

D. *The allergic response of the meninges.* The capacity of the meninges to manifest "delayed hypersensitivity" in the form of an acute exudative reaction suggests that this may be an important mechanism in the development of increased intracranial pressure and subarachnoid block. Burn and Finley produced a severe exudative meningitis in guinea pigs with visceral tuberculosis by the intrathecal administration of tuberculoprotein; normal controls did not become ill.[28] These experiments were the forerunner of those of Swithbank, Smith, and Vollman who described an acute nonbacterial meningitis in Mantoux-positive patients given PPD intrathecally.[171] Clinically, these patients, who were described as having an "intrathecal tuberculin reaction," developed fever, headache, and nuchal rigidity. The CSF showed pleocytosis and elevation in protein, and the blood-CSF barrier became more permeable to bromide.[160] The intensity of the response was directly proportional to the amount of tuberculin administered and the sensitivity of the host; Mantoux-negative individuals did not develop meningitis, and, conversely, the severity of the reaction was ameliorated following desensitization. There is little doubt that the intrathecal tuberculin reaction is an allergic response of the meninges. Whether it of any importance in tuberculous meningitis or whether delayed hypersensitivity to other bacteria is responsible for the formation of exudate in the subarachnoid space is not known. Exudation produced in this manner may not be entirely detrimental since, in some instances at least, intrathecal tuberculin has been effective in relieving subarachnoid block in patients with tuberculous meningitis.[5, 159]

E. *Immunity.* The role of specific immunity in bacterial meningitis has been studied extensively. In the pre-antibiotic era, introduction of specific antisera into the subarachnoid space was of some benefit in experimental meningococcal, pneumococcal, and hemophilus meningitis.[60, 62, 109, 198] With the exception of some enthusiastic reports,[61a, 187] the results in man were unimpressive.[66a] There is some evidence that the combination of specific rabbit antiserum and sulfonamides exerted a synergistic effect in hemophilus infection of the meninges.[14]

Normally, there is little or no transfer of antibody from the blood into the spinal fluid.[11, 80, 104] Using a more sensitive technique, Freund demonstrated antibody in the CSF of rabbits actively and passively immunized with typhoid bacilli.[69] The ratio of blood to CSF antibody titers in actively immunized animals was 300 : 1, which was quantitatively similar to the ratio of serum to CSF gamma globulin determined by electrophoretic techniques.[91] The blood-CSF and blood-brain barriers may differ in their permeability to immune particles, and the localization of antibody in the brain is not necessarily accompanied by a rise of the same antibody in the spinal fluid.[69, 71]

Passage of antibody into the CSF is enhanced during aseptic meningitis and has been demonstrated for neutralizing substances to poliomyelitis[64, 66] and meningococcal agglutinins.[8] Similarly, hemolysins to sheep red cells and complement have also been found in the CSF of patients with meningitis, but not in normals.[187, 188]

In view of the precipitous onset and brief duration of bacterial meningitides, active immunity may not be acquired in time to influence the outcome of these acute infections. Furthermore, as in subacute bacterial endocarditis, patients with bacterial meningitis may have antibodies to the offending pathogen in the circulation. This suggests that antibody does not reach adequate concentration in the CSF, even in meningitis. An alternative explanation, suggested by the relative ineffectiveness of antisera therapeutically, is that the subarachnoid space provides a poor environment for the action of antibody.

There is a considerable body of evidence, however, that acquired immunity is an important factor in man's resistance to meningitis. Specific examples are furnished by *H. influenzae* meningitis which is confined almost exclusively to children between 3 and 18 months of age. Fothergill tested blood from newborns and children of various ages for bactericidal activity against *H. influenzae* and demonstrated that blood from infants under two months and children older than three years killed the organisms regularly, while that obtained from children between these ages was but weakly bactericidal.[66b] Susceptibility of infants to *H. influenzae* meningitis appears to be directly related to the absence of antibody and with the development of active

immunity, presumably on repeated exposure to the organism in the respiratory tract, the host is afforded almost permanent protection from infection with this bacterium. Similarly, the occurrence of meningococcal meningitis is largely determined by the immune state of the host. A case in point is the relatively high incidence of this disease in unseasoned Army recruits. In contrast, clinical cases are extremely rare in sailors at sea where the population turn-over is low.[10a] Acquisition of specific immunity appears to be instrumental in preventing second attacks of meningococcal and hemophilus meningitis which are quite rare. In fact, most recurrent attacks of bacterial meningitis are caused by pneumococcus and, even in this situation, different types are usually incriminated.[81b, 173b]

There is a group of conditions in which man appears peculiarly vulnerable to meningeal infections. Among these are congenital and acquired agammaglobulinemia, in which there appears to be a tendency to develop coccal meningitis,[71a] multiple myeloma, which is frequently complicated by pneumococcal infections including meningitis, and surgical or congenital absence of the spleen, in which pneumococcal meningitis has been a frequent occurrence.[72a, 87a, 158b] In the first two instances, gamma globulin is diminished or functionally defective, and antibody production is markedly impaired. The reason for susceptibility of splenectomized children to infection in general, and meningitis in particular, is not readily apparent. These patients are capable of synthesizing gamma globulin normally, and the concentration of this protein fraction in the serum is normal or elevated. Furthermore, they have a normal response following a provocative dose of diphtheria toxoid.[158b] On the other hand, Rowley demonstrated that splenectomized patients failed to respond with a significant titer following the intravenous administration of sheep erythrocytes, a challenge which was regularly associated with a brisk antibody response in normal experimental subjects.[151a]

It is fair to say, on the basis of these observations, that immune processes are of considerable importance in determining man's susceptibility to meningeal infection. The precise conditions under which these protective mechanisms are operative and the stimuli evoking the appearance of antibody in the nervous system remain subjects for further investigation.

F. *Fever.* Elevation of body temperature does little to disturb the equilibrium between the brain and CSF and the rest of the body unless extreme heights are reached. No change in radioactive phosphorus exchange was found in rabbits with temperatures ranging between 38.2 C. and 41.0 C.[58] Earlier studies indicated that permeability to bismuth and hemolysins to sheep red cells, but not trypan blue, was increased in rabbits with fevers of 42 C.-43 C.[164] In man, elevation of the temperature to 106 F. for

30 minutes on five consecutive days resulted in an increased transfer of bromide from blood to CSF.[180]

Whether the blood brain barrier is permeable to substances which are themselves capable of producing fever has been the subject of considerable study.[141] There is some evidence that endogenous pyrogen, which is presumably the end-product of cellular injury by a variety of pyrogenic stimuli, gains access to the meninges with ease; in contrast, bacterial endotoxins which consist of large lipopolysaccharide molecules gain entry into the CNS only after a considerable delay. King and Wood have interpreted these data to mean that endogenous pyrogen is the substance responsible for activating the thermoregulatory centers,[99] but there are also experiments which suggest that, in the absence of endogenous pyrogen, bacterial endotoxins may affect these centers directly.[141]

COMMENT

It seems clear that a review of this nature will pose more questions than it answers. Without reiterating any specific points, it is still not clear how microorganisms enter the meninges, how infections begin, and what defenses the host mobilizes to combat infection. The unique behavior of various species of bacteria, the mechanisms governing the biochemical alterations in the spinal fluid, and the role of normal constituents of the body fluids in meningeal infection remain unsolved. Entirely shrouded in mystery are the nature of the histochemical and enzymatic defects which must be a part of the profound inflammatory reaction. More pragmatically, the mechanism of death occurring in the face of a bacteriologically sterile spinal fluid remains undefined. If this report has stimulated sufficient interest in these biological phenomena to promote a return of the subject of bacterial meningitis from the historical library to the laboratory, it will have served its purpose.

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